CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074623

Trade Name : LACTULOSE SOLUTION USP 10GM/15ML

Generic Name: Lactulose Solution USP 10Gm/15ml

Sponsor : Pharmaceutical Associates, Inc.

Approval Date: July 30, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074623

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074623

APPROVAL LETTER

ANDA 74-623

JUL 30 1996

Pharmaceutical Associates, Inc.
Attention: Kaye B. McDonald
P.O. Box 128
Conestee, SC 29636

Dear Madam:

This is in reference to your abbreviated new drug application dated February 16, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Lactulose Solution USP, 10 g/15 mL.

Reference is also made to your amendments dated June 4 and 10, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Lactulose Solution USP, 10 g/15 mL bioequivalent and, therefore, therapeutically equivalent to the listed drug Chronulac Syrup of Hoescht Marion Roussel, Inc.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 7/30/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074623

FINAL PRINTED LABELING

APPROVED JUL 30 1996

NDC 0121-0577-30

LACTULOSE SOLUTION, USP 20 g/30 mL

Each 30 mL contains: 20 g lactulose (and less than 3.2 g galactose, less than 2.4 g lactose, and 2.4 g or less of other sugars). Also contains FD&C Yellow No. 6, water, and flavoring. Sodium hydroxide used to adjust pH. The pH range is 3.0 to 7.0.
INDICATIONS: For the treatment of constipation. See insert labeling for full information.

Usual Adult Dosage: 1 to 2 tablespoonfuls (15 to 30 mL) daily. See Insert.
Since lactulose does not exert its effect until it reaches the colon, and since transit time through the colon may be slow, 24 to 48 hours may be required to produce a normal bowel movement. Some patients have found that lactulose solution may be more acceptable when mixed with fruit juice, water, or milk.
Product may darken slightly but therapeutic action is not affected. Do not use if extreme darkening or turbidity occurs. See accompanying product information.
CAUTION: Federal law prohibits dispensing without prescription.
This unit dose package is not child-resistant. Store at controlled room temperature, 15° to 30°C (59° to 86°F). Do not freeze.
PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

APPROVED

UNIT DOSE
Delivers 30 mL
NDC 0121-0577-30
LACTULOSE
SOLUTION USP 20g/30mL
Indications: For the treatment of constipation. See Insert
Expiration Date and Lot No.

CAUTION: Federal law prohibits dispensing without prescription

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

JUL 30 1996

LACTULOSE SOLUTION, USP
20 g / 30 mL
10 Unit Dose Cups of 30 mL each

APPROVED

Usual Adult Dosage: 1 to 2 tablespoonfuls (15 to 30 mL) daily. See accompanying product information.
Indications: For the treatment of constipation. See insert for full information.
Since lactulose does not exert its effect until it reaches the colon, and since transit time through the colon may be slow, 24 to 48 hours may be required to produce a normal bowel movement.
Some patients have found that lactulose solution, USP may be more acceptable when mixed with fruit juice, water, or milk.

NDC 0121-0577-08

LACTULOSE SOLUTION, USP
10 g/15 mL

Each 15 mL contains: 10 g lactulose (and less than 1.6 g galactose, less than 1.2 g lactose, and 1.2 g or less of other sugars). Also contains FD&C Yellow No. 6, water, and flavoring. Sodium hydroxide used to adjust pH. The pH range is 3.0 to 7.0.
Dispense in original container or tight, light-resistant container with child-resistant closure.
To the Pharmacist: When ordering this product, include the product number (or NDC) in the description.
CAUTION: Federal law prohibits dispensing without prescription

8 fl oz (237 mL)

PHARMACEUTICAL ASSOCIATES, INC.
Greenville, SC 29605

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JUL 30 1996

Store at controlled room temperature, 15° to 30°C (59° to 86°F). Do not freeze.
Product may darken slightly but therapeutic action is not affected. Do not use if extreme darkening or turbidity occurs. See accompanying product information.
Keep tightly closed.

Expiration Date and Lot No.

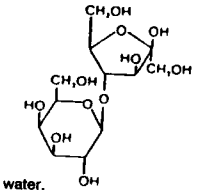
Lactulose Solution, USP
10 g/15 mL

DESCRIPTION

Lactulose is a synthetic disaccharide in solution form for oral administration. Each 15 mL of Lactulose Solution contains: 10 g lactulose (and less than 1.6 g galactose, less than 1.2 g lactose, and 1.2 g or less of other sugars). Also contains FD&C Yellow No. 6, water, and flavoring. Sodium hydroxide used to adjust pH. The pH range is 3 to 7.

Lactulose is a colonic acidifier which promotes laxation.

The chemical name for lactulose is 4-0-ß-D-galactopyranosyl-D-fructofuranose. It has the following structural formula:



$C_{12}H_{22}O_{11}$

The molecular weight is 342.30. It is freely soluble in water.

CLINICAL PHARMACOLOGY

Lactulose is poorly absorbed from the gastrointestinal tract and no enzyme capable of hydrolysis of this disaccharide is present in human gastrointestinal tissue. As a result, oral doses of lactulose solution reach the colon virtually unchanged. In the colon, lactulose is broken down primarily to lactic acid, and also to small amounts of formic and acetic acids, by the action of colonic bacteria, which results in an increase in osmotic pressure and slight acidification of the colonic contents. This in turn causes an increase in stool water content and softens the stool. Since lactulose does not exert its effect until it reaches the colon, and since transit time through the colon may be slow, 24 to 48 hours may be required to produce the desired bowel movement.

Lactulose solution given orally to man and experimental animals resulted in only small amounts reaching the blood. Urinary excretion has been determined to be 3% or less and is essentially complete within 24 hours.

INDICATIONS AND USAGE

For the treatment of constipation. In patients with a history of chronic constipation, lactulose solution therapy increases the number of bowel movements per day and the number of days on which bowel movements occur.

CONTRAINDICATIONS

Since lactulose solution contains galactose (less than 1.6 g/15 mL), it is contraindicated in patients who require a low galactose diet.

WARNINGS

A theoretical hazard may exist for patients being treated with lactulose solution who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. Accumulation of H_2 gas in significant concentration in the presence of an electrical spark may result in an explosive reaction. Although this complication has not been reported with lactulose, patients on lactulose therapy undergoing such procedures should have a thorough bowel cleansing with a non-fermentable solution. Insufflation of CO_2 as an additional safeguard may be pursued but is considered to be a redundant measure.

PRECAUTIONS

General: Since lactulose solution contains galactose (less than 1.6 g/15 mL) and lactose (less than 1.2 g/15 mL), it should be used with caution in diabetics.

Information for Patients: In the event that an unusual diarrheal condition occurs, contact your physician.

Laboratory Tests: Elderly, debilitated patients who receive lactulose solution for more than six months should have serum electrolytes (potassium, chloride, carbon dioxide) measured periodically.

Drug Interactions: Results of preliminary studies in humans and rats suggest that nonabsorbable antacids given concurrently with lactulose may inhibit the desired lactulose-induced drop in colonic pH. Therefore, a possible lack of desired effect of treatment should be taken into consideration before such drugs are given concomitantly with lactulose solution.

Carcinogenesis, Mutagenesis, Impairment of Fertility
There are no known human data on long-term potential for carcinogenicity, mutagenicity, or impairment of fertility.
There are no known animal data on long-term potential for mutagenicity.
Administration of lactulose solution in the diet of mice for 18 months in concentrations of 3 and 10 percent (V/W) did not produce any evidence of carcinogenicity.
In studies in mice, rats, and rabbits, doses of lactulose syrup up to 6 or 12 mL/kg/day produced no deleterious effects in breeding, conception, or parturition.

Pregnancy

Teratogenic Effects

Pregnancy Category B:
Reproduction studies have been performed in mice, rats, and rabbits at doses up to 3 or 6 times the usual human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to lactulose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lactulose solution is administered to a nursing woman.
Pediatric Use:
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
Precise frequency data are not available.
Initial dosing may produce flatulence and intestinal cramps, which are usually transient. Excessive dosage can lead to diarrhea with potential complications such as loss of fluids, hypokalemia, and hypernatremia.
Nausea and vomiting have been reported.

OVERDOSAGE

Signs and Symptoms
There have been no reports of accidental overdosage. In the event of overdosage, it is expected that diarrhea and abdominal cramps would be the major symptoms. Medication should be terminated.

Oral LD_{50}
The acute oral LD_{50} of the drug is 48.8 mL/kg in mice and greater than 30 mL/kg in rats.

Dialysis
Dialysis data are not available for lactulose. Its molecular similarity to sucrose, however, would suggest that it should be dialyzable.

DOSAGE AND ADMINISTRATION:
The usual dose is 1 to 2 tablespoonfuls (15 to 30 mL, containing 10 g to 20 g of lactulose) daily. The dose may be increased to 60 mL daily if necessary. Twenty-four to 48 hours may be required to produce a normal bowel movement.
Note: Some patients have found that lactulose solution may be more acceptable when mixed with fruit juice, water or milk.

Approved
11 30

HOW SUPPLIED
NDC 0121-0577-30
30 mL unit dose cups in trays of 10 cups
NDC 0121-0577-08
8 fl oz bottles
Lactulose solution contains lactulose 667 mg/mL (10 g/15 mL).
Store at controlled room temperature, 15° to 30°C (59° to 86°F). Do not freeze.
Under recommended storage conditions, a normal darkening of color may occur. Such darkening is characteristic of sugar solutions and does not affect therapeutic action. Prolonged exposure to temperatures above 30°C (86°F) or to direct light may cause extreme darkening and turbidity which may be pharmaceutically objectionable. If this condition develops, do not use.
Prolonged exposure to freezing temperatures may cause change to a semisolid, too viscous to pour. Viscosity will return to normal upon warming to room temperature.
Keep tightly closed.
Dispense in original container or tight, light-resistant container with child-resistant closure.
To the Pharmacist: When ordering this product, include the product number (or NDC) in the description.
CAUTION: Federal law prohibits dispensing without prescription.

Pharmaceutical Associates, Inc.
Greenville, S.C. 29605

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074623

CHEMISTRY REVIEW(S)

1. CHEMIST REVIEW NO. 3

2. ANDA # 74-623

3. NAME AND ADDRESS OF APPLICANT
Pharmaceuticals Associates, Inc.
Division of Beach Products, Inc.
Attention: Ms. Kaye B. McDonald
201 Delaware St. at Perimeter Rd.
Greenville, South Carolina 29605

Mailing:
P.O. Box 128
Conestee, S.C. 29636

4. LEGAL BASIS for ANDA SUBMISSION
Chronulac® solution is not entitled to a period of marketing exclusivity under section 505(j)(4)(D) of the Act and the pertinent patent has expired.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Lactulose

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

February 16, 1995--	Original Submission
April 4, 1995--	Telecom--Ms. Parise
April 4, 1995--	Telecom--New Correspondence
April 4, 1995--	Acknowledgement letter
May 1, 1995--	Labeling review
July 19, 1995--	Deficiency letter
July 24, 1995--	New correspondence
September 12, 1995-	Bio waiver granted
December 13, 1995-	Amendment
May 29, 1996--	Deficiency letter
June 4, 1996--	Amendment
June 10, 1996--	Telecom
June 10, 1996--	Telecom Amendment

10. PHARMACOLOGICAL CATEGORY
Laxative

11. Rx or OTC
Rx

12. RELATED DMFs

(b)4 - Confidential Business

(b)4 - Confidential Business

13. DOSAGE FORM
Solution

14. POTENCY
10g/15mL

15. CHEMICAL NAME AND STRUCTURE
4-O-Beta-D-Galactopyranosyl-D-fructose; 4-D-galactopyranosyl-4-D-fructoruranose; 4-O-Beta-galactosyl-D-fructose; 4-Beta-D-galactoside-D-fructose. C12H22O11, molecular weight 342.30.

16. RECORDS AND REPORTS
None

17. COMMENTS
An annual report was filed with DMF (b)4 on 2/19/96. The subject was reviewed on 7/17/96 and found to be acceptable. However, a letter will be issued requesting further clarification.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter issue.

19. REVIEWER:
Edwin Ramos

/S/

DATE COMPLETED:
June 14, 1996

7/22/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074623

BIOEQUIVALENCE REVIEW(S)

SEP 12 1995

Lactulose Syrup, USP.
10 Gm/15 ml
ANDA **#74-623**
Review: Ramona M. Hawkins
File: 74623W.295

Pharmaceutical Associates, Inc.
Conestee, South Carolina
Submission Dated:
February 16, 1995

Review of a Waiver Request

This submission provides a request for a waiver of in-vivo bioequivalence study requirements for this product under the provisions of 21 CFR 320.22 (b)(3). The product contains the same active and inactive ingredients as Marion Merrell Dow's Chronulac (lactulose syrup) as follows:

Each 15ml contains:

Ingredients	Chronulac (MMD)	Lactulose Syrup (Pharm'l Assoc.)
Lactulose, USP	10.0gm	10.0gm
Galactose		
Lactose		
Other Sugars		
Fructose		
Epilactose		
FD&C Blue No. 1		
FD&C Yellow No. 6		
[redacted]Pineapple Orange Blend		
Sodium Hydroxide N.F.	To a	
	3.	
Purified Water, USP. qs to	15ml.	15ml.

(b)4 - Confidential Business

Comment

As can be seen from the comparison above, this product meets the criteria of 21 CFR 320.22 (b)(3) in that it has the same formulation, with the active ingredients in the same concentration and dosage form and the same strength as that of the reference product. The product contains no inactive ingredient or other changes in formulation from the drug production that is the subject of an approved full new drug application that significantly affect absorption of the active drug ingredient or active moiety. Accordingly, the waiver may be granted. The firm should be so advised.

Recommendation

The firm should be advised as follows:

The Division of Bioequivalence agrees that the information submitted by Pharmaceutical Associates, Inc. demonstrates that Lactulose Syrup, USP., 10Gm/15ml., falls under the provisions of 21 CFR 320.22(b)(3) of the Bioequivalence/Bioavailability Regulations. The waiver of the in - vivo bioequivalence study requirement for Lactulose Syrup, USP., 10Gm/15ml. (test product) is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product to be bioequivalent to Chronulac (lactulose syrup), 10Gm/15ml, manufactured by Marion Merrell Dow.

/S/

Ramona McCarthy Hawkins
Review Branch I
Division of Bioequivalence

RD INITIALED YCHUANG
FT INITIALED YCHUANG /S/ Date: 8/15/95

Concur: /S/ Date: 9/12/95

K
Director
Division of Bioequivalence

cc: ANDA #74-623 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, McCarthy), Drug File, Division File

RHM/dbm/72595/74623W.295

SEP 12 1995

Lactulose Syrup, USP.
10 Gm/15 ml
ANDA #74-623
Review: Ramona M. Hawkins
File: 74623W.295

Pharmaceutical Associates, Inc.
Conestee, South Carolina
Submission Dated:
February 16, 1995

Review of a Waiver Request

This submission provides a request for a waiver of in-vivo bioequivalence study requirements for this product under the provisions of 21 CFR 320.22 (b)(3). The product contains the same active and inactive ingredients as Marion Merrell Dow's Chronulac (lactulose syrup) as follows:

Each 15ml contains:

Ingredients	Chronulac (MMD)	Lactulose Syrup (Pharm'l Assoc.)
Lactulose, USP	10.0gm	10.0gm
Galactose	(b)4 - Confidential Business	
Lactose		
Other Sugars		
Fructose		
Epilactose		
FD&C Blue No. 1		
FD&C Yellow No. 6		
[redacted]Pineapple Orange		
Sodium Hydroxide N.F.		
Purified Water, USP. qs to	15ml.	15ml.

Comment

As can be seen from the comparison above, this product meets the criteria of 21 CFR 320.22 (b)(3) in that it has the same formulation, with the active ingredients in the same concentration and dosage form and the same strength as that of the reference product. The product contains no inactive ingredient or other changes in formulation from the drug production that is the subject of an approved full new drug application that significantly affect absorption of the active drug ingredient or active moiety. Accordingly, the waiver may be granted. The firm should be so advised.

Recommendation

The firm should be advised as follows:

The Division of Bioequivalence agrees that the information submitted by Pharmaceutical Associates, Inc. demonstrates that Lactulose Syrup, USP., 10Gm/15ml., falls under the provisions of 21 CFR 320.22(b)(3) of the Bioequivalence/Bioavailability Regulations. The waiver of the in - vivo bioequivalence study requirement for Lactulose Syrup, USP., 10Gm/15ml. (test product) is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product to be bioequivalent to Chronulac (lactulose syrup), 10Gm/15ml, manufactured by Marion Merrell Dow.

/S/

Ramona McCarthy Hawkins
Review Branch I
Division of Bioequivalence

RD INITIALED YCHUANG /S/
FT INITIALED YCHUANG

Date: 8/15/95

Concur: /S/

Date: 9/12/95

Keith Chan, Ph. D.
Director
Division of Bioequivalence

cc: ANDA #74-623 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, McCarthy), Drug File, Division File

RHM/dbm/72595/74623W.295